

FORM PTO-1390 (REV. 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER <b>GJE-6035</b>	
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>				U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <div style="font-size: 1.5em; font-family: monospace;">09/913814</div>	
INTERNATIONAL APPLICATION NO. <b>PCT/GB00/00630</b>		INTERNATIONAL FILING DATE <b>22 February 2000</b>		PRIORITY DATE CLAIMED <b>22 February 1999</b>	
TITLE OF INVENTION <b>Rapidly-Soluble Compositions</b>					
APPLICANT(S) FOR DO/EO/US <b>Glen Patrick Martyn and Camilo Colaco</b>					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
<ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</li> <li>4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</li> <li>5. <input type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))           <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input checked="" type="checkbox"/> has been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).           <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto.</li> <li>b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</li> </ol> </li> <li>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))           <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input type="checkbox"/> have been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).</li> <li>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)) <u>unsigned</u>.</li> <li>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ol>					
<b>Items 11 to 20 below concern document(s) or information included:</b>					
<ol style="list-style-type: none"> <li>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.</li> <li>14. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>15. <input type="checkbox"/> A substitute specification.</li> <li>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 37 CFR 1.821 - 1.825.</li> <li>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</li> <li>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</li> <li>20. <input type="checkbox"/> Other items or information:</li> </ol>					

U.S. APPLICATION NO. <b>09/913814</b> <small>(37 CFR 1.53)</small>	INTERNATIONAL APPLICATION NO. PCT/GB00/00630	ATTORNEY'S DOCKET NUMBER GJE-6035
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21. ☒ The following fees are submitted:

**BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):**

Neither international preliminary examination fee (37 CFR 1.482)  
 nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO  
 and International Search Report not prepared by the EPO or JPO. .... **\$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to  
 USPTO but International Search Report prepared by the EPO or JPO ..... **\$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO  
 but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... **\$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO  
 but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... **\$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO  
 and all claims satisfied provisions of PCT Article 33(1)-(4) ..... **\$100.00**

**ENTER APPROPRIATE BASIC FEE AMOUNT =**

Surcharge of **\$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30  
 months from the earliest claimed priority date (37 CFR 1.492(e)).

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$
Total claims	<b>10</b> - 20 =	<b>0</b>	x <b>\$18.00</b>	
Independent claims	<b>1</b> - 3 =	<b>0</b>	x <b>\$80.00</b>	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ <b>\$270.00</b>
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$860.00</b>
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				+
<b>SUBTOTAL =</b>				<b>\$860.00</b>
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				
<b>TOTAL NATIONAL FEE =</b>				<b>\$860.00</b>
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property +				
<b>TOTAL FEES ENCLOSED =</b>				<b>\$860.00</b>
				Amount to be refunded:
				\$
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				\$

**CALCULATIONS PTO USE ONLY**

a. ☐ A check in the amount of \$ \_\_\_\_\_ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-0065 in the amount of \$ 860.00 to cover the above fees.  
 A duplicate copy of this sheet is enclosed.

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 overpayment to Deposit Account No. 19-0065. A duplicate copy of this sheet is enclosed.

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 information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR  
 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

CORRESPONDENCE ADDRESS:

CUSTOMER NUMBER

23,557

August 17, 2001

DATE

*David Saliwanchik*

SIGNATURE

David R. Saliwanchik

NAME

31,794

REGISTRATION NUMBER

09933034-1091902  
518 Rec'd PCT/PTO 17 AUG 2001  
09/913814

August 17, 2001

Patent Application

Docket No. GJE-6035

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Glen Patrick Martyn and Camilo Colaco  
Docket No. : GJE-6035  
For : Rapidly-Soluble Compositions

PRELIMINARY AMENDMENT

Please amend the above-identified patent application as follows:

In the Specification

After page 11: Please insert as new page 12 the attached Abstract of the Disclosure.

In the claims

Please amend the claims to read as follows:

Claim 2 (amended):

The composition according to claim 1, wherein the carbohydrate polymer is hydroxyethyl starch.

Claim 3 (amended):

The composition according to claim 1, wherein the carbohydrate polymer is pollulan.

Claim 4 (amended):

The composition according to claim 1, which comprises at least one excipient.

Claim 5 (amended):

The composition according to claim 1, which comprises a low molecular weight carbohydrate.

Claim 6 (amended):

The composition according to claim 1, which comprises a component selected from colouring agents and flavouring agents.

Claim 7 (amended):

The composition according to claim 1, which comprises a therapeutic agent.

Claim 8 (amended):

The composition according to claim 1, in the shape of a tablet.

Claim 9 (amended):

The composition according to claim 1, obtainable by the removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape.

Claim 10 (amended):

The composition according to claim 9, wherein the removal of solvent comprises freeze-drying.

Remarks

Claims 2-10 have been amended.

No new matter has been added by these amendments.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Respectfully Submitted



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DRS/la

Attachment: Marked-up Version of Amended Claims  
New page 12 (Abstract of the Disclosure)

Marked-up Version of Amended ClaimsClaim 2 (amended):

[A] The composition according to claim 1, wherein the carbohydrate polymer is hydroxyethyl starch.

Claim 3 (amended):

[A] The composition according to claim 1, wherein the carbohydrate polymer is pollulan.

Claim 4 (amended):

[A] The composition according to [any preceding claim] claim 1, which comprises at least one excipient.

Claim 5 (amended):

[A] The composition according to [any preceding claim] claim 1, which comprises a low molecular weight carbohydrate.

Claim 6 (amended):

[A] The composition according to [any preceding claim] claim 1, which comprises a component selected from colouring agents and flavouring agents.

Claim 7 (amended):

[A] The composition according to [any preceding claim] claim 1, which comprises a therapeutic agent.

Claim 8 (amended):

[A] The composition according to [any preceding claim] claim 1, in the shape of a tablet.

Claim 9 (amended):

[A] The composition according to [any preceding claim] claim 1, obtainable by the removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape.

Claim 10 (amended):

[A] The composition according to claim 9, wherein the removal of solvent comprises freeze-drying.



### Abstract of the Disclosure

A composition in the form of a shaped body, comprises a rapidly soluble, open matrix of a carbohydrate polymer. Such a composition may be obtained by the removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mold corresponding to the desired shape.

RAPIDLY-SOLUBLE COMPOSITIONSField of the Invention

The present invention relates to rapidly-soluble compositions. The compositions are suitable for use as vehicles for the delivery, e.g. the mucosal or oral delivery, of bioactive substances. The compositions are also suitable for use as delivery vehicles for active substances requiring rapid release.

Background of the Invention

The most common pharmaceutical dosage form is the tablet. The main limitations of tablets are poor patient compliance due to the difficulty in swallowing tablets and the difficulty in achieving effective dissolution, to release the bioactive contents. Thus, there is a need for rapidly-soluble compositions. A number of approaches have been used, including effervescent tablets using a variety of volatile material-generating systems, chewable tablets, disintegrants and wicking agents.

More recently, therapeutic compositions have been formulated using rapidly-soluble matrices. These are especially useful for oral administration, such as for the lingual, sublingual or buccal delivery of drugs. The current most commercially popular form is described in US-A-4305502 and US-A-4754597, in which rapidly-soluble solid dosage forms are made by aliquoting a slurry of therapeutic agent, solvent, gelatin and other excipients into preformed depressions. The liquid is then frozen and the solvent removed by sublimation, typically freeze-drying. The resulting tablet has an open porous matrix that dissolves rapidly on contact with saliva at body temperature in the mouth. This dosage form, marketed by R.P.Scherer as Zydis®, has enjoyed commercial success, for instance, as in the Feldene Melt® tablets distributed by Pfizer.

This type of delivery vehicle allows rapid dissolution of the delivery vehicle on exposure to moisture. Consequently, the tablet dissolves almost immediately upon contact with mucosal surfaces. Although this format enjoys

a large market, it has the drawback of containing gelatin. Gelatin has the potential of contamination and is unsuitable for the treatment of vegetarians. The hygroscopicity of this gelatin formulation also means that Zydis® tablets have to be stored in moisture-resistant packs. The tablets quickly give rise to an unacceptable "sticky" mouth-feel resulting from the poor solubility of gelatin below 37°C, and accentuated by moisture uptake of the freeze-dried gelatin. Following buccal delivery, the mouth should not be washed out for 3-5 minutes.

EP-A-0357665 and US-A-4855326 describe therapeutic vehicles made from cotton candy. These have the advantages, of cost and simpler, more flexible processing, over Zydis® tablets. However, there are significant problems with the development of validated methods of compacting the candy floss into tablets and with the hygroscopicity of the tablets formed. Further, the tablets exhibit much slower dissolution than Zydis®, which precludes their use in buccal delivery formats which are possible with the latter.

US-A-4623394 discloses compressed tablets comprising pullulan and a gum-like heteromannan. The intention is to provide gradual disintegration. Even in a control experiment, without the heteromannan, the compressed tablet took over 2 hours to achieve 100% release.

#### Summary of the Invention

The present invention is based on the surprising discovery that pullulan or HES (hydroxyethyl starch) can satisfactorily be used as a replacement for gelatin, in tablets of the Zydis® type. This is despite the fact that attempts to use most carbohydrates and carbohydrate polymers, to form such matrices, including those proposed as potential substitutes for gelatin in the prior art, did not result in the production of tablets that were comparable to Zydis®. Pullulan (which is described herein by way of example only) provided instantaneous dissolution and stability at ambient temperatures and humidities, thus

enabling its use in solid delivery forms as well as reducing the requirements and costs for water-resistant packaging for such delivery forms.

More particularly, it has been found that a rapidly  
5 soluble, open matrix of a carbohydrate polymer can be formed by removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape. It appears that  
10 materials such as pullulan can readily provide a shaped body that is not only readily invaded by water, but also low friability.

#### Description of the Invention

The present invention encompasses methods of making  
15 rapidly-soluble matrices of sugar (of which pullulan is an example, used herein for illustration) capable of dissolution in minimal volumes of aqueous solvent and of sufficient structural integrity to be handled as discrete units containing actives. These products are suitable for  
20 use in any applications that require fast-dissolving solid formulations. They are particularly suitable for use in mucosal delivery formulations, such as tablets for per-oral delivery, that dissolve in saliva.

In one embodiment, pullulan, any necessary or  
25 desirable excipients and active agent to be delivered are mixed in a liquid (in which one or more of the components may be soluble), frozen, e.g. in individual dosage aliquots, and then lyophilised, to remove the solvent and yield a rapidly-soluble matrix containing the active. The  
30 water or other solvent may also be removed by sublimation or evaporation. If desired, the liquid may be frozen as part of a continuous process of lyophilisation.

Products of the invention comprise matrices that are  
soluble not just at body temperatures but also at ambient  
35 and lower temperatures. They are thus suitable not just for oral or buccal delivery as solid matrices but also as soluble matrices for rapid dissolution in aqueous solvent

prior to administration. The latter formulations may be combined with other excipients and formulations that aid rapid disintegration and dissolution of solid matrices including effervescent couples.

5       A wide variety of bioactive materials are suitable for use in accordance with the present invention, including therapeutic and prophylactic agents. The delivery vehicle and methods of the present invention provide for a variety of dosing schemes for delivery of the bioactive material  
10       and are suitable for both veterinary and human applications.

Any suitable excipient may be used. Many examples will be well known to those skilled in the art. Criteria for the choice of excipients include their effects on the  
15       process for obtaining the rapidly-soluble matrix, or the physical or organoleptic characteristics of the matrix. For example, the product is a confectionery product and the excipients may include flavoring agents, food dyes, stabilisers and the like. Alternatively, the product is a  
20       therapeutic composition comprising pharmaceutical excipients as well as biologically active agents such as drugs.

Excipients suitable for use herein include other carbohydrates including sugars, sugar alcohols, straight-  
25       chain polyalcohols and non-reducing glycosides of polyhydroxy compounds. The preferred sugar alcohols are mannitol and xylitol. The glycosides are preferably monoglycosides, in particular the compounds obtained by reduction of disaccharides such as lactose, maltose,  
30       lactulose and maltulose. The glycosidic group is preferably a glucoside or a galactoside and the sugar alcohol is preferably sorbitol (glucitol). Examples include maltitol (4-O- $\beta$ -D-glucopyranosyl-D-glucitol), lactitol (4-O- $\beta$ -D-galactopyranosyl-D-glucitol), iso-  
35       maltulose, palatinit (a mixture of GPS,  $\beta$   $\alpha$ -D-glucopyranosyl-1-6-sorbitol, and GPM,  $\alpha$ -D-glucopyranosyl-1-6-mannitol), and its individual sugar

alcohols, the components GPS and GPM. Suitable carbohydrates include, but are not limited to, lactose,  $\alpha\alpha,\beta,\beta$  and  $\alpha,\beta$ -trehaloses, raffinose, palatinit, GPS, stachyose, mellibiose and mannotriose. In the case of a delivery vehicle, the excipients can include those found in confectionaries.

The presence of a low molecular weight carbohydrate, e.g. a mono-, di-, tri- or tetrasaccharide, can enhance the dissolution properties of a product of this invention.

The amount of therapeutic (or bioactive) agent should be sufficient to yield a final product that contains an effective amount of the therapeutic agent. The products obtained are suitable for use as pharmaceuticals, other medical applications such as diagnostics, environmental applications, agricultural and industrial use. An effective amount of a bioactive agent is one which causes amelioration or palliation of the condition to be treated. Such amounts are known in the art and readily determinable.

Examples of types of bioactive materials that can be used in the invention include any pharmaceutical agents, including anti-inflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, anti-depressants, antipsychotics, tranquilisers, anti-anxiety drugs, narcotic antagonists, anti-Parkinsonism agents, cholinergic agonists, chemotherapeutic drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistaminics, anti-migraine agents, coronary, cerebral or peripheral vasodilators, hormonal agents, contraceptives, antithrombotic agents, diuretics, antihypertensive agents, cardiovascular drugs and opioids.

Suitable bioactive materials also include biological modifiers. Such modifiers include subcellular compositions, cells, bacteria, viruses and molecules including lipids, organics, proteins and peptides (synthetic and natural), peptide mimetics, hormones (peptide, steroid and corticosteroid), D and L amino acid polymers,

oligosaccharides, polysaccharides, nucleotides, oligonucleotides and nucleic acids, including DNA and RNA, protein-nucleic acid hybrids, small molecules and physiologically active analogues thereof. Further, the  
5 modifiers may be derived from natural sources or made by recombinant or synthetic means and include analogues, agonists and homologues.

As used herein "protein" refers also to peptides and polypeptides. Such proteins include enzymes,  
10 biopharmaceuticals, growth hormones, growth factors, insulin, monoclonal antibodies, interferons, interleukins and cytokines. Organics include pharmaceutically active chemicals with amino, imino and guanidino groups. Suitable steroid hormones include estrogen, progesterone,  
15 testosterone and physiologically active analogues thereof. Numerous steroid hormone analogues are known in the art and include estradiol, SH-135 and tamoxifen. Many steroid hormones such as progesterone, testosterone and analogues thereof are particularly suitable for use in the present  
20 invention as they are destroyed upon oral administration by the so-called hepatic first-pass mechanism. As used herein, "nucleic acids" includes any therapeutically effective nucleic acids known in the art including DNA, RNA and physiologically active analogues thereof. The  
25 nucleotides may encode single genes or may be any vector known in the art of recombinant DNA including plasmids, retroviruses and adeno-associated viruses. Preferably, the nucleotides are administered in the powder form of the solid dose vehicle.

30 Compositions containing prophylactic bioactive materials and carriers therefore are further encompassed by the invention. Preferred compositions include immunogens such as vaccines. Suitable vaccines include live and attenuated viruses, nucleotide vectors encoding antigens,  
35 heat-shock protein complexes, bacteria, antigens, antigens plus adjuvants, and haptens coupled to carriers. Particularly preferred are vaccines effective against

diphtheria, tetanus, pertussis, botulinum, cholera, Dengue, Hepatitis A, C and E, hemophilus influenza B, herpes virus, *Helicobacter pylori*, influenza, Japanese encephalitis, meningococci A, B and C, measles, mumps, papilloma virus, pneumococci, polio, rubella, rotavirus, respiratory syncytial virus, *Shigella*, tuberculosis, yellow fever and combinations thereof. Vaccines may also be produced by molecular biology techniques to produce recombinant peptides or fusion proteins containing one or more portions of a protein derived from a pathogen. For instance, fusion proteins containing the antigen of interest and the B subunit of cholera toxin have been shown to induce an immune response to the antigen of interest. See Sanchez et al (1989), Proc. Natl. Acad. Sci. USA 86:481-485.

Preferably, the immunogenic composition contains an amount of an adjuvant sufficient to enhance the immune response to the immunogen. Suitable adjuvants include aluminum salts, squalene mixtures (SAF-1), muramyl peptide, saponin derivatives, mycobacterium cell wall preparations, heat-shock proteins, monophosphoryl lipid A, mycolic acid derivatives, nonionic block copolymer surfactants, Quil A, cholera toxin B subunit, polyphosphazene and derivatives, and immunostimulating complexes (ISCOMs) such as those described by Takahashi et al (1990), Nature 344:873-875.

For veterinary use and for the production of antibodies in animals, mitogenic components of Freund's adjuvant can be used. As with all immunogenic compositions, the immunologically effective amounts of the immunogens must be determined empirically. Factors to be considered include the immunogenicity, whether or not the immunogen will be complexed with or covalently attached to an adjuvant or carrier protein or other carrier, route of administration and the number of immunising doses to be administered. Such factors are known in the vaccine art and it is well within the skill of immunologists to make such determinations without undue experimentation.



The present invention encompasses compositions and methods of making the compositions. Although singular forms may be used, more than one carbohydrate polymer and more than one excipient and active substance may be present. Determination of the effective amounts of these compounds is within the skill of one in the art.

Methods for lyophilising solutions to produce solid matrices are known in the art and have been described in, for example, US-A-4305502, US-A-4754597 and Rey et al (1975), Proc. R. Soc. Lond. B. Biol. Sci. 191:9-19. Conventional freeze-drying equipment can be used. Such equipment is commercially available, for example, from Edwards, FTS or Virtis. Alternatively, any equipment may be used that achieves the effect of producing freeze-dried products. Removal of solvent can be by sublimation and/or evaporation. For production of the rapidly-soluble solid matrices by lyophilisation, freezing can be carried out as a separate step or incorporated into the lyophilisation process. The exact processing conditions will be depend on the formulation and equipment and can be readily determined by one skilled in the art. Excipients may be added to enhance the processing and/or to tailor the physical or organoleptic properties of the compositions that are obtained.

The following Examples illustrate the invention.

Example 1

0.25, 0.5, 1 and 2.5% solutions of pullulan (PI-20, Hayashibara Co.) or HES in water containing 5% mannitol, raffinose or trehalose were dispensed into 1 ml aliquots into the wells of a plastic blister pack (Boots Ltd). The blisters were loaded into a Heto freeze-drier and frozen on the shelf held at -32°C before turning on the vacuum and lyophilising the frozen solution for 24 h (ramping from -20°C to 30°C) to yield a solid matrix of carbohydrate polymer plus sugar excipient. All the formulations used yielded intact solid matrices in the blister packs which dissolved instantaneously in water at room temperature

(15-20°C), even after a week's storage of the blisters on the bench at ambient temperatures and humidities. Only the matrices containing 1 or 2.5% carbohydrate polymer were of sufficiently low friability to be removed as an intact single dosage unit from the wells of the blister pack.

#### Example 2

Solutions containing 5% pullulan (PI 20, Hayashibara Co.), 5% mannitol and 20% diltiazem (model hydrophilic active) were dispensed into 1 ml aliquots into the wells of a plastic blister pack (Boots Ltd). The blisters were flash-frozen at -70°C and then loaded into a Heto freeze-drier (shelf held at -10°C) and lyophilised for 4 h (ramping from -10°C to 60°C) to yield a solid matrix of carbohydrate polymer plus sugar excipient. The solid matrices in the blister packs were of sufficient non-friability (3.52%) to be removed as an intact single dosage unit from the wells of the blister pack and dissolved instantaneously in water (<2sec) at room temperature (15-20°C), even after a week's storage of the blisters on the bench at ambient temperatures and humidities. In comparison, the friability of commercial Zydis® tablets was 2.8% and the dissolution time c.8 sec. The mean water content of the solid matrices was 3.24% (SD 0.19%) and the mean content uniformity of active 98.62% (SD 0.73%).

#### Example 3

The procedure of Example 2 was repeated, but using, instead of diltiazem, 20% acyclovir (model hydrophobic active). The solid matrices obtained in the blister packs were of sufficient non-friability (2.69%) to be removed as an intact single dosage unit from the wells and dissolved instantaneously in water (<2sec) at room temperature (15-20°C), even after a week's storage of the blisters on the bench at ambient temperatures and humidities. The mean water content of the solid matrices was 4.75% (0.11%) and the mean content uniformity of active 105.63% (SD 0.96%).

Although the foregoing invention has been described in some detail by way of illustration and example for purposes

of clarity of understanding, it will be apparent to those skilled in the art that certain changes and modifications may be practised. Therefore, the description and examples should not be construed as limiting the scope of the invention, which is delineated by the appended claims.

CLAIMS

1. A composition in the form of a shaped body, comprising a rapidly soluble, open matrix of a carbohydrate polymer.
2. A composition according to claim 1, wherein the carbohydrate polymer is hydroxyethyl starch.
3. A composition according to claim 1, wherein the carbohydrate polymer is pullulan.
4. A composition according to any preceding claim, which comprises at least one excipient.
5. A composition according to any preceding claim, which comprises a low molecular weight carbohydrate.
6. A composition according to any preceding claim, which comprises a component selected from colouring agents and flavouring agents.
7. A composition according to any preceding claim, which comprises a therapeutic agent.
8. A composition according to any preceding claim, in the shape of a tablet.
9. A composition according to any preceding claim, obtainable by the removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape.
10. A composition according to claim 9, wherein the removal of solvent comprises freeze-drying.

12

11. A composition according to claim 3, in the form of a shaped body that is rapidly soluble in water, comprising a therapeutic agent and, as a vehicle, an open matrix of pullulan.

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**PCT**

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 9/20</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/50013</b> <b>(43) International Publication Date:</b> 31 August 2000 (31.08.00)
<b>(21) International Application Number:</b> PCT/GB00/00630 <b>(22) International Filing Date:</b> 22 February 2000 (22.02.00) <b>(30) Priority Data:</b> 9904049.5                      22 February 1999 (22.02.99)                      GB <b>(71) Applicant (for all designated States except US):</b> QUADRANT HOLDINGS CAMBRIDGE LIMITED [GB/GB]; 1 Mere Way, Ruddington, Nottingham NG11 6JS (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MARTYN, Glen, Patrick [GB/GB]; Quadrant Holdings Cambridge Limited, 1 Mere Way, Ruddington, Nottingham NG11 6JS (GB). COLACO, Camilo [GB/GB]; 107 Foster Road, Cambridge CB2 2JN (GB). <b>(74) Agent:</b> GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> RAPIDLY-SOLUBLE COMPOSITIONS  <b>(57) Abstract</b>  A composition in the form of a shaped body, comprises a rapidly soluble, open matrix of a carbohydrate polymer. Such a composition may be obtained by the removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape.		

USA

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on an invention entitled  
**RAPIDLY-SOLUBLE COMPOSITIONS**

the specification of which ☐ is attached hereto or

☐ was filed on 22 FEB 2000 as United States Application Number or PCT International Application Number PCT/GB00/00630 and was amended on 15 MAR 2001 (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for a patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

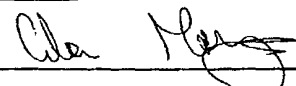
Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
9904049.5	GB	22 FEB 1999	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: David R. Saliwanchik, Reg. 31,794; Jeff Lloyd, Reg. 35,589; Doran R. Pace, Reg. 38,261; Christine Q. McLeod, Reg. 36,213; Jay M. Sanders, Reg. 39,355; James S. Parker, Reg. 40,119 and Jean E. Kyle, Reg. 36,987; Frank C. Eisenschenk, Reg. 45,332; Seth M. Blum. Reg. 45,489

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

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I hereby certify that this correspondence is a  
facsimile transmitted to the U.S. Patent and  
Trademark Office on the date shown below:

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#2

Patent Application  
Docket No. GJE-6035  
Serial No. 09/913,814

September 19, 2002

David R. Saliwanchik  
David R. Saliwanchik, Patent Attorney

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Glen Patrick Martyn and Camilo Colaco  
Serial No. : 09/913,814  
Filed : August 17, 2001  
For : Rapidly-Soluble Compositions

Box PCT/MISSING REQUIREMENTS  
Assistant Commissioner for Patents  
Washington, D.C. 20231

TRANSMITTAL LETTER

Sir:

The Applicants have not received a Notification of Missing Requirements Under 35 U.S.C. 371 from the United States Designated/Elected Office (DO/EO/US). However, the Applicants are transmitting herewith an executed Declaration and Power of Attorney form for the above-referenced application.

Please charge the surcharge of \$130 for the late-filed Declaration (37 CFR 1.63) to Deposit Acct. No. 19-0065. The Commissioner is hereby authorized to charge any additional fees that may be required to Deposit Account No. 19-0065.

Respectfully submitted,

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Attachments: Executed Declaration (37 CFR 1.63) and Power of Attorney form

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